REMARKS

This Amendment is in response to the Examiner's Final Office Action mailed on January 1, 2005. Claim 22 has been amended. Claims 22, 26, 27, and 43-46 are now pending. Applicants submit that the Amendment puts the claims in condition for allowance or in a better form for consideration on appeal. Because Applicants filed a Notice of Appeal on April 4, 2005, Applicants hereby submit a two-month extension of time. Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks.

I. Interview of June 16, 2005

Applicants' representatives Shirley Chen and Eric Witt thank Examiner Goldberg for the courtesy extended to them in the interview of June 16, 2005. The discussion and suggestions presented in that interview are reflected in the present amendment and remarks.

II. Rejection of Claims 22, 26 and 27 Under 35 U.S.C. §103(a)

Claims 22, 26, and 27 stand rejected as allegedly unpatentable under 35 U.S.C. §103(a)over Weinberger et al. ("Weinberger") in view of Mbayed et al. ("Mbayed") and further in view of Yoshida et al. ("Yoshida") or Oon et al. ("Oon"). Applicants respectfully traverse the Examiner's rejection based on the following reasons.

To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Independent claim 22 as amended specifies that a set of first and second primers ~~having~~ consisting of SEQ ID NO: 1 and SEQ ID NO: 2, respectively are used in the claimed method for

for evaluating whether a sample contains HBV that may have escaped immunological detection of HBV surface antigen (HBsAg),

Although claim 22 has been amended to include the closed transition term "consisting of" rather than "having" as it was previously, Applicants respectfully maintain their previous submission that claim 22, as previously submitted, was not obvious because the elements of a prima facie case of obviousness were not present. However, in an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection Applicants have amended claim 22 to specify the sequences of the primer set.

The cited references in combination do not render the claimed invention obvious because the first requirement of a prima facie case of obviousness that all the limitations of the claim be disclosed or suggested in the cited art has not been met. The Office has conceded that "Weinberger does not specifically teach using primers of SEQ ID NO: 1 and 2. Weinberger further does not specifically teach that each mutation at 130, 131, 133, and 145 are mutations which may be used to detect a sample contains HBV that has escaped immunological detection of HbsAG." Paper 1204, page 4.

The Office relies on Mbayed to supply the limitation of "a set of first and second primers ~~having~~ consisting of SEQ ID NO: 1 and SEQ ID NO: 2." The Office further relies on Yoshida or Oon to supply the limitation of "having a mutation at amino acid position 130, from glycine to aspartic acid, or at amino acid position 131 from threonine to asparagine;" (claim 22), as well as "having a mutation at position 133 from methionine to threonine." (claim 26) or "having a mutation at position 145 from glycine to arginine." (claim 27). Mbayed does not disclose or suggest the missing limitation of "consisting of SEQ ID NO: 1 and SEQ ID NO: 2." Nor do Yoshida or Oon disclose the missing limitations of the specified mutations.

Mbayed does not disclose primers consisting of SEQ ID NO: 1 and 2. The Office has stated that "SEQ ID NO:1 of the instant application comprises each of the 20 nucleotides of [Mbayed primer] HBS1 with an additional T nucleotide on the 3' end. [Mbayed primer] HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application, namely four nucleotides downstream at 694-713." Thus, the Office has itself admitted that neither of the closest primers disclosed by Mbayed consists of SEQ ID NO: 1 and 2, as required by the present claim 22.

Applicants further respectfully note that Mbayed HBS2 primer is not, as stated by the Office, four nucleotides downstream of SEQ ID NO: 2. The 5' end of Mbayed HBS2 primer is offset from the 3' end of SEQ ID NO: 2 by four nucleotides (the two primers have no overlap), but the 3' end of the Mbayed HBS2 primer is actually over 27 nucleotides downstream from the 3' end of SEQ ID NO:2. This gives a more precise picture of the difference between the two primers. Not only are the disclosed HBS1 and HBS2 primers not the same as the primers recited in claim 22, (especially with the closed "consisting of" language) but HBS2 is not consistent with even open-ended claim language, since it does not share any common sequence with SEQ ID NO: 2.

Because Mbayed does not disclose primers consisting of (or even comprising) SEQ ID NO: 1 and 2, Mbayed instead is relied on to suggest primers of SEQ ID NO: 1 and 2. The Office has argued that "The ordinary artisan would have been motivated to have amplified using SEQ ID NO: 1 and 2 since the claimed oligonucleotides, namely SEQ ID NO: 1 and 2, simply represent functional equivalents to the primers taught in the art by Mbayed, the skilled artisan would have been motivated to have designed additional primers which amplified HBV nucleic acids." Paper 1204, pp. 5-6, emphasis added. The amended claim recites that the primers consist of SEQ ID NO: 1 and 2. In order for Mbayed to suggest these primers, the ordinary artisan must have been led to the use of specific primers of SEQ ID NO: 1 and 2 by the work of Mbayed. However, not only would the ordinary artisan not have found SEQ ID NO: 1 and 2 to have been suggested by Mbayed, the ordinary artisan would not have been led to use any different primers than those used by Mbayed, let alone the pair specified by the claim language requiring that the primers "consist of" SEQ ID NO: 1 and 2.

This is because the primers used in Mbayed are not a functional equivalent of the primer set in claim 22. The function of the primers used in Mbayed is distinctly different from the function of the primers of claim 22, and in fact at odds with using the primers of claim 22. The function of Mbayed is for phylogenetic analysis: the comparison of HBV sequences from different geographic regions in order to "determine the molecular epidemiology of HBV in the pediatric population." Mbayed, p. 3362, first column; see also phylogenetic tree depicted in Fig. 2 of Mbayed. Thus, Mbayed is not directed to mutation detection per se, nor to detection of mutations "indicating that the sample contains HBV that may have escaped immunological

detection of HBsAg," as recited in claim 22. Instead, Mbayed is directed at phylogenetic analysis.

Due to the very nature of phylogenetic analysis of a population, Applicants submit that Mbayed does not suggest that its primers be changed be same as SEQ ID NO: 1 and 2 recited in claim 22. Phylogenetic analysis is not aimed at detection of new mutations, or even at improved detection of known mutations. Rather, it is directed to comparison of different populations, which requires that samples from different populations be treated, as much as possible, in precisely the same manner. In this way, any variations between populations can be attributed to true genetic variation, and not to differences in sample handling and preparation. Thus, one of ordinary skill would not find that other primers are suggested by the primers of Mbayed. Indeed, quite the opposite: one of ordinary skill would be very cautious about making any changes at all in the procedure of Mbayed, let alone anything so central to genotyping as the choice of primers. To change the primers from those used in the study of Mbayed would be to weaken any conclusions drawn from the genotypic data, as one could no longer be certain that procedural variations were not contributing to variations seen in genotyping. This is arguably true even for a one nucleotide difference, such as between HBS1 and SEQ ID NO: 1, and is indisputably true for an offset of over 25 nucleotides and no shared sequence, such as between HBS2 and SEQ ID NO: 2.

Furthermore, with the present "consisting of" transitional language, it is difficult to see how one of ordinary skill in the art would have discerned any suggestion in Mbayed, Weinberger, or the other cited art, to use the specified primers of the claim. The Office has stated "The claims are drawn to primers having SEQ ID NO: 1 and 2. Having is open claim language which allows for additional sequences on either end of SEQ ID NO: 1 and 2." Paper 1204, p. 11. The claims now contain the closed language "consisting of," and this argument is not relevant to the present claims. Given the completely different function of the primers of Mbayed compared to the specific primers of claim 22, any possible suggestion to change the primers to be specifically and precisely the same as SEQ ID NO: 1 and 2 vanishes completely.

There would also be no motivation to combine the Weinberger and Mbayed references. Again, this is because they are directed at completely different endpoints. Weinberger states that

its purpose is to examine the hypothesis that "mutations in the HBsAg itself and especially in its "a" determinant which is exposed at the surface of HBsAg particles and recognized by anti-HBVs, may render the particles undetectable by conventional immunological assays." Weinberger, p. 138, column 2. To test the hypothesis, Weinberger used a primer set of [ ] which are positioned far away from the positions of HBV genome targeted by SEQ ID NO: 1 and 2. Nowhere in this reference is there a teaching or suggestion of using a primer set such as the one in claim 22. Indeed, the Office relies on Mbayed to suggest the primers of claim 22 precisely because there would be no motivation in Weinberger itself to suggest the primers.

However, as noted above, Mbayed is directed to phylogenetic analysis. One of ordinary skill would not have been motivated to combine the two, as the purpose of the primers of Mbayed (which are not the primers of claim 22)—namely, to provide a consistent method of amplifying known mutations sample-to-sample—was distinctly different from the purpose of Weinberger—namely, to test as accurately as possible a hypothesis about mutations. In order to combine Weinberger and Mbayed to achieve the primers of the claims, one of skill in the art would have to have 1) been motivated to modify the primers of Mbayed to precisely match the primers recited in claim 22, then 2) use those precise, specific primers for the purpose of Weinberger. As discussed above, due to the distinctly different purposes of testing between Mbayed and Weinberger the motivation of the ordinary artisan would have been away from making the modification of 1); nor would there have been a motivation to use the specific primers for the purpose of Weinberger, as in 2).

In addition, Yoshida is not prior art to the instant application, and thus each and every limitation of claim 26 is not disclosed in the cited art, and claim 26 is not obvious in view of the cited art. The prima facie publication date of Yoshida is October, 2000. The present application claims priority to Singapore patent application No. 200004041, filed July 18, 2000, thus predating the publication date of Yoshida The Office has stated that "A certified copy of the application has been provided. Should the applicant desire to obtain the benefit of foreign priority . . . a translation of the foreign application should be submitted . . . ." Applicants note that the certified copy of the application provided to the Office was in English; thus, a translation is not necessary to establish priority. For the Examiner's convenience and reference, Applicants submit herewith a copy of the priority document SG 200004041.

As the publication date of Yoshida is after the priority date of the present application, Yoshida is not prior art to the present application. The Office relies on Yoshida for disclosure of a Met133Thr mutation and an Asn131Thr mutation, and on Oon for disclosure of a Gly130Asp mutation and a Gly145Arg mutation. With Yoshida eliminated as prior art, the limitation of claim 26 of "determining whether the amplified product comprises nucleic acid encoding major HBV surface antigen (SHBsAg) having a mutation at position 133 from methionine to threonine," is not disclosed among the mutations of Oon. Thus, in addition to the failure of Mbayed and Weinberger to disclose every element of claim 22, each and every limitation of claim 26 is not disclosed by the cited references, and claim 26 is not prima facie obvious in view of the cited art.

In view of the failure of the cited references to teach or suggest the claimed invention, Applicants submit that a prima facie case of obviousness has not been established under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is respectively requested.

III. Rejection of Claim 43 Under 35 U.S.C. §103(a)

Claim 43 stands rejected under 35 USC 103(a) as being unpatentable over Weinberger in view of Mbayed and further in view of Yoshida or Oon, and further in view of Mason.

As discussed in detail above, independent claim 22 as amended specifies a method for detecting a HBV strain that may have escape immunological detection of HBsAg through detection of a mutation in SHBsAg at amino acid position 130 from glycine to aspartic acid, or at amino acid position 131 from threonine to asparagine.

None of Weinberger, Mbayed. and Yoshida or Oon teaches or suggests the claimed invention. Mason et al. merely teaches reverse transcribing HBV RNA.

Thus, the cited references, each alone or in combination, fail to teach or suggest the claimed method. Claim 43 is therefore not only novel but also non-obvious under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is therefore respectively requested.

IV. Rejection of Claims 44-46 Under 35 U.S.C. §103(a)

Claims 44-46 stand rejected under 35 USC §103(a) as being unpatentable over Weinberger in view of Mbayed and further in view of Yoshida or Oon, and further in view of Dattagupta.

As discussed in detail above, independent claim 22 as amended specifies a method for detecting a HBV strain that may have escape immunological detection of HBsAg through detection of a mutation in SHBsAg at amino acid position 130 from glycine to aspartic acid, or at amino acid position 131 from threonine to asparagine.

None of Weinberger, Mbayed. and Yoshida or Oon. teaches or suggests the claimed invention. Dattagupta *et al.* merely teaches immobilizing amplification primers on a substrate.

Thus, the cited references, each alone or in combination, fail to teach or suggest the claimed method. Claims 44-46 are therefore not only novel but also non-obvious under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is therefore respectively requested.

CONCLUSION

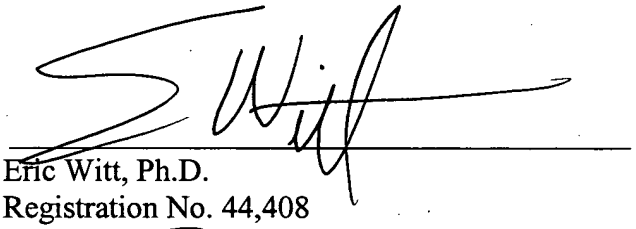
Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit Examiner to expedite prosecution of this patent application to issuance. Should Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 20781-703).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Date: July 5, 2005

By: 

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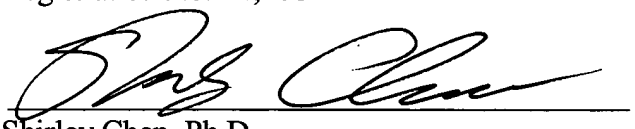
By: 

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